REMARKS

Claims 48-132 were previously pending in this application. Claims 48, 55, 63, 77, 80, 86, 100, 102, 109, 118 and 132 have been amended. Claim 101 has been canceled. Furthermore, new claims 133-182 have been added above. Accordingly, claims 48-100 and 102-182 are presented for further examination on the merits.

The title of the invention has been changed to reflect the subject matter now being claimed, which includes the compositions, apparatus and new array claims. Claim 101 was drawn to a kit and has now been canceled. The new title reflects the cancellation of that kit claim.

The specification has been amended in several instances to correct informalities related to the use of the trademark TRITON X-100. The affected portions in the specification include page 18, 8th line from the bottom; page 24, lines 9-10, 22 and 30; and page 25, line 2. As astutely noted by the Examiner in the January 21, 1998 Office Action (page 7), the use of the trademark should be capitalized and accompanied by the generic terminology. Accordingly, the generic term "octoxymol" has been inserted five times after each recitation of the TRITON X-100 trademark. The term "octoxymol" is taken from The Merck Index, Tenth Edition, entry 6601, page 971; copy attached hereto as Exhibit 1.

In a sincere effort to define their invention more clearly, Applicants have amended each of claims 48, 55, 63, 77, 80, 86, 100, 102, 109, 118 and 132 hereinabove. With respect to the independent claims, 48, 77, 100, 102 and 132, these claims have been amended to recite the soluble signal as a positive element. In claims 48 and 77 which are drawn to compositions of matter, one of the double-stranded oligonucleotide or polynucleotide "produces a soluble signal generated or generatable from a chemical label or labels which comprise a signalling moiety or moieties." Similarly, in the system defined by claim 102, the oligonucleotide or polynucleotide recites "in double-stranded form producing a soluble signal generated or generatable from a chemical label or labels which comprise a signalling moiety or moieties." In all three claims, 48, 77 and 102, the fluid or solution element has been incorporated into the system, the latter being recited as

"a transparent non-porous or translucent non-porous system containing a fluid or solution." In effect, the "capable" language with respect to both the system and the soluble signal has been altogether removed from the pending claims. Similarly, the apparatus claims, 100 and 132, have been amended to remove the "capable" language in favor of a more positive recitation of the "soluble signal."

Commensurate with their broad and complete disclosure, Applicants are now claiming "porous glass" as an embodiment for "glass or glass-coated surface" recited variously in claims 54, 79 and 108. Thus, new dependent claims 133 and 134 have been added above. Both recite . . . "wherein said glass or glass-coated surface comprises porous glass." Support for "porous glass" is drawn from the specification, Example 1, pages 15-16, the latter page citing Weetal and Filbert, "Porous Glass for Affinity Chromatography Applications," Methods in Enzymology, Volume XXXIV, pages 59-72, W. B. Jakoby and M. Wilchek, editors.

In claims 55, 80 and 109, as well as new claims 135-137, Applicants are claiming "plastic or plastic-coated surface" as embodiments for the non-porous polymeric material. Support for "plastic-coated surface" is drawn from the language of originally filed claim 39 from the first-filed application in the family, U.S. Patent Application Serial No. 06/491,469, filed on January 21, 1983. Original claim 39 defined "[a] substrate in accordance with Claim 1 wherein said substrate is a plastic-coated substrate." To conform the "plastic-coated surface" language with the pending claims, Applicants have also added new dependent claims 135-137. Each of these new claims recites a composition "wherein said non-porous polymeric material comprises plastic or a plastic-coated surface." Thus, the progression followed in the claims presented herein is that of a "non-porous polymeric material" (claims 53 and 78 and 107), the non-porous polymeric material being "plastic or a plastic-coated surface" (claims 135, 136 and 137), and the plastic or plastic-coated surface being selected from . . . "polyethylene, polypropylene, polystyrene and epoxy" (claims 55, 80 and 109).

In three other amended claims, 63, 86 and 118, Applicants have clarified the Markush members by deleting reference to a "DNA-RNA chimera." After that deletion, the remaining members include "DNA, RNA and a DNA-RNA hybrid, or a combination of any of the foregoing." Support in the original disclosure for "DNA-RNA hybrid" is described in further detail below in the new matter rejection under

35 U.S.C. §112, first paragraph, *infra*.

In addition to the above-mentioned amendments to the claims, Applicants have canceled claim 101. The cancellation of this claim has been done in a sincere effort to narrow the issues in the present prosecution, particularly with respect to the obviousness-type double patenting rejection set forth on page 7 of the January 21, 1998 Office Action and discussed *infra*.

Finally, commensurate with their complete and broad disclosure, Applicants have added new claims 141-182 which are directed to an array of substrate surfaces, the array comprising a plurality of nucleic acid strands fixed or immobilized to the substrate surfaces. It is believed that the presentation of these new claims is fully supported by the original disclosure and comprises subject matter to which Applicants are duly entitled to claim. Entry of new claims 141-182 is respectfully urged.

Related Japanese Patent Application No. 14165/84

Applicants would like to bring to the attention of the Patent Office and the Examiner recent developments in the Japanese Patent Office (JPO) regarding related Japanese Patent Application No. 14165/84, which is based upon the priority document, 06/491,469, filed on January 21, 1983. Their Japanese associates have recently informed the Assignee that although not formally allowed, the pending claims in that Japanese application are expected to be allowed by the end of the summer. A copy of the Japanese associates' April 22, 1998 letter and the pending claims 1-73 are attached hereto as Exhibits 2 and 3, respectively.

Before proceeding to the substantive issues in the January 21, 1998 Office Action, Applicants acknowledge, with appreciation, the indication by the Examiner that rejections and/or objections not reiterated from previous office actions have been withdrawn. Applicants are confident that the remaining issues will be further narrowed by this paper, if not resolved altogether.

The Rejection for New Matter Under 35 U.S.C. §112, First Paragraph

Claims 53, 54, 60, 63, 77-99, 101, 107, 108, 114 and 118 stand rejected under 35 U.S.C. 112, first paragraph, as containing new matter. In the January 21, 1998 Office Action (pages 2-3), the Examiner stated:

> **[1]** Claims 53, 78, and 107 contain NEW MATTER in that "siliceous matter" is cited. Consideration of the instant disclosure as filed has failed to reveal written basis for this phrase. It is noted that glass is disclosed as filed but not the broader phrase "siliceous matter". This broadening in scope is NEW MATTER. **[2]** Similarly claims 54, 79, and 108 contain the phrase "glass-coated surface" which lacks written basis as filed.
>
> **[3]** Claims 63, 86, and 118 contain NEW MATTER because there is no written basis as filed for either DNA-RNA hybrid or a DNA-RNA chimera.
>
> **[4]** Consideration of the disclosure as filed has failed to reveal the limitation of instant claims 60 and 114 directed to the support and system being composed of different materials. This limitation is therefore NEW MATTER.
>
> **[5]** Claims 77-85 and 87-99 contain NEW MATTER because the oligonucleotide or polynucleotide is cited as fixed or immobilized to the system rather than being limited to being fixed or immobilized to the solid support within such a system. Consideration of the disclosure as filed has not revealed fixing or immobilizing to a system as now cited in claims 77 etc.
>
> **[6]** Claim 101 cites the phrase "instructions therefor" in the last line. Consideration of the disclosure as filed has failed to reveal written basis for any such instructions which therefore causes claim 101 to contain NEW MATTER.
>
> The above NEW MATTER rejections are either reiterated or necessitated by amendment.

The rejection for new matter is respectfully traversed.

In order to ensure that each and every ground is thoroughly addressed, bold bracketed numbers have been inserted above in the Examiner's remarks. The points which follow below are directed to those bracketed numbers.

[1] With respect to "siliceous matter" in claims 53, 78, and 107, Applicants respectfully submit that this language is altogether supported by the original disclosure. A review of the first-filed application, Serial No. 06/491,469 (filed on January 21, 1983), reveals at least three instances where the term "siliceous" is used in conjunction with "substrate," or other words, including but not limited to

the following: page 24, lines 1-2 ("siliceous materials"); lines 4-5 ("siliceous substrates"); and originally filed claim 4 ("glass or other siliceous material").

[2] Regarding the recitation of "glass-coated surface" in claims 54, 79 and 108, it is submitted that this terminology is also supported by the original disclosure. More specifically, the language "glass-coated substrate" is found in originally filed claim 40 ("A substrate in accordance with Claim 1 wherein said substrate is a glass-coated substrate"). Because under the law the claims are part of the disclosure, original claim 40 is sufficient proper support for the instant recitation of "glass-coated surface" in both the pending and new claims.

[3] Concerning the issue of "DNA-RNA hybrid" and a "DNA-RNA chimera" in claims 63, 86 and 118, Applicants have proceeded to meet the Examiner's position halfway, so to speak. In the case of the latter recitation, Applicants have expunged the reference of a "DNA-RNA chimera" altogether from the claim language. In the case of a "DNA-RNA hybrid, it is believed that this language is fully supported by the original disclosure. In the originally filed claims, for example, claim 33 recites "[a] substrate in accordance with Claim 1 wherein said double-stranded polynucleotide comprises as one of the strands polydeoxyribonucleotide and the other strand a polyribonucleotide." Thus, the language at hand, "DNA-RNA hybrid," should be deemed supported by Applicants' original disclosure.

[4] Concerning the language in claims 60 and 114 that the solid support and system are "composed of different materials," Applicants respectfully maintain that the original disclosure clearly supports this embodiment. At the outset, the disclosure and the pending independent claims, notably claims 48, 77 and 102, describe or define the system as being "transparent non-porous or translucent non-porous." In contrast, the solid support can be porous or non-porous, and this is described in the original disclosure. For example, on page 10 (first full paragraph) in Applicants' U.S. Patent Application Serial No. 06/732,374, filed on May 9, 1985, that was a continuation-in-part to the seminal application (Serial No. 06/461,469), it is disclosed:

> . . . In the practices of this invention, it is preferred that the solid support to which the analyte is fixed be non-porous and transparent, such as glass, or alternatively, plastic, polystyrene, polyethylene, dextran, polypropylene and the like. Conventional porous materials,

> e.g., nitrocellulose filters, although less desirable for practice of the method of the present invention, may also be employed as a support.

Thus, the disclosure is clear that the system is non-porous and that the solid support can be porous, thus conveying to the ordinarily skilled artisan, that the system and solid support can be composed of different materials.

Moreover, in Example 1 (pages 15-16) in that same application (Serial No. 06/732,374), Applicants disclose the use of porous glass as a solid support, citing a 1974 publication previously cited of record in this application **[insert footnote]** [Weetall, H. H. and Filbert, A. M., "Porous Glass for Affinity Chromatography Applications," Methods in Enzymology, Volume XXXIV, Affinity Techniques: Part B, Edited by Jakoby, W. B. and Wilchek, M., 1974, pages 59-72]. Taken with the fact that the system is non-porous in every instance, the use of porous glass in Example 1 for the solid support must reasonably convey to the ordinarily skilled artisan that the system and the solid support can be composed of quite different materials.

In the event that further assurance is needed that the disclosure reasonably conveys to the skilled artisan that Applicants were in possession of the subject matter of claims 60 and 114 at the time their application was filed, the Examiner is invited to read the Declaration of Dr. Dean L. Engelhardt in Support of Possession of Claimed Subject Matter and Novelty of Invention which is being concurrently filed herewith as Exhibit 4. In Paragraphs 6 and 7 of his Declaration (Exhibit 4), Dr. Engelhardt declares that in his opinion, the specification supports and adequately describes the aforementioned embodiments wherein the solid support and the system are composed of different materials. According to Dr. Engelhardt, the support and description in the specification would have reasonably conveyed to one skilled in the relevant art to which the present invention pertains that the inventors were in possession of this subject matter at the time the application was filed.

As noted in Dr. Engelhardt's Declaration, the specification discloses that the system for containing or retaining a fluid or solution, be it a product, device, apparatus, wells, tubes, cuvettes, and the like, can be transparent non-porous or translucent non-porous, and that the solid support can be non-porous or porous. Dr. Engelhardt continues in Subparagraph A of Paragraph 7:

On page 14, second paragraph, there is disclosed " . . . a device containing a portion for retaining a fluid." Later in the that paragraph, it is disclosed that "[t]he portion of the device for containing the fluid is desirably a well, a tube, or a cuvette." Also disclosed in the same paragraph is " . . . an apparatus comprising a plurality of such devices for containing a fluid, in which at least one such device contains the above-described immobilized polynucleotide sequence, polynucleotide or oligonucleotide probe, signalling moiety, and soluble signal." On page 13, last paragraph, there is disclosed:

> Yet another aspect of the method of the present invention involves generating the soluble signal from the probe-analyte hybrid in a device capable of transmitting light therethrough for the detection of the signal by spectrophotometric techniques.

In Subparagraph B, Dr. Engelhardt continues:

The specification also discloses that the solid support can be non-porous and transparent as well as conventional porous materials. For example, on page 10, the first full paragraph, it is disclosed:

> . . . In the practices of this invention, it is preferred that the solid support to which the analyte is fixed be non-porous and transparent, such as glass, or alternatively, plastic, polystyrene, polyethylene, dextran, polypropylene and the like. Conventional porous materials, e.g., nitrocellulose filters, although less desirable for practice of the method of the present invention, may also be employed as a support.

In Subparagraph C, Dr. Engelhardt writes:

In the above-quoted portion, the specification plainly indicates that the solid support can be made of non-porous and transparent materials, such as glass and plastic, or conventional porous materials, such as nitrocellulose filters. In other portions, for example, page 14, second paragraph, the specification also indicates that the system, e.g., a product, device, apparatus, wells, tubes, cuvettes, and the like, are in every instance made of non-porous materials for containing or retaining a fluid or solution. Thus, the specification would reasonably convey to one skilled in the relevant art that at the time the application was filed the inventors were in possession of the subject matter of claims 60 and 114 wherein the solid support and the system are made or composed of different materials.

And in SubParagraph D of his Declaration, Dr. Engelhardt indicates that his opinion is further bolstered by the claim language in several of the originally filed

claims:

> . . . The following original claims support the language of claims 60 and 114 with respect to the system and the solid support are composed of different materials:
>
> claim 5 (" . . . characterized in that said solid support is non-porous,");
> claim 8 (" . . . characterized in that said solid support is porous.");
> claim 16 (" . . . wherein said detecting step further comprises generating said soluble signal in a device capable of transmitting light therethrough for the detection of said soluble signal by spectrophotometric techniques.");
> claim 17 (. . . characterized in that said device is selected from the group consisting of a well, a tube, a cuvette and an apparatus which comprises a plurality of said wells, tubes or cuvettes."); and
> claim 21 (. . . wherein said means for containing a fluid is selected from the group consisting of a well, a tube, and a cuvette.").

In the first full paragraph on page 6 of his Declaration, Dr. Engelhardt concludes: "From a reading of the above-quoted original claims and/or the specification quoted above in Paragraphs 7A and 7B, one skilled in the relevant art would reasonably conclude that the inventors were in possession at the time the application was filed of the claimed subject matter wherein the system and the solid support are composed of different materials."

[5] Regarding support for claims 77-85 and 87-99 wherein the oligonucleotide or polynucleotide is fixed or immobilized to the system rather than to a solid support within the system, it is respectfully submitted that the disclosure is fully supportive of such subject matter. On page 14 (full paragraph) in Serial No. 06/732,374, Applicants disclose:

> A further aspect of the present invention provides products useful in the disclosed method for detection of a polynucleotide sequence. Among these products is a **device containing a portion for retaining a fluid. Such portion contains an immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe**. The probe, as described above, has covalently attached thereto a chemical label including a signalling moiety capable of generating a soluble signal. Also part of the device is a soluble signal, preferably a colored or fluorescent product, generatable by means of the signalling moiety. The portion of the device for containing the fluid is desirably a well, a tube, or a cuvette. A related product of the invention is an apparatus comprising a plurality of such devices for containing a fluid, in which at least one such device contains the above-described immobilized polynucleotide sequence, polynucleotide or oligonucleotide probe, signalling moiety, and soluble signal. . . [bold added]

Originally filed claim 20 in Serial No. 06/732,374 also defines the

aforedescribed device in which an oligonucleotide or polynucleotide is fixed or immobilized to the system (or a device, a device belonging to the genus system). Original claim 20 recites:

> 20. A device which comprises:
> means for containing a fluid comprising:
> (i) an immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe, said probe having covalently attached thereto a chemical label comprising a signalling moiety capable of generating a soluble signal, and
> (ii) a soluble signal generated by means of said signalling moiety.

In the view of the above-quoted portion from the specification and original claim 20, withdrawal of the new matter rejection with respect to claims 77-85 and 87-99 is respectfully requested.

Applicants respectfully point out that Dr. Engelhardt's Declaration (Exhibit 4) also addresses the issue of new matter with respect to claims 77-85 and 87-99. In Paragraph 8 of his Declaration, Dr. Engelhardt declares that it is his position that the specification discloses that the oligonucleotide or polynucleotide is fixed or immobilized to the system and as such, does not limit the present invention to having the oligonucleotide or polynucleotide fixed or immobilized to a solid support within the system. Dr. Engelhardt continues in the same paragraph:

> The subject matter of claims 77-85 and 87-99 specifically calls for a composition of matter comprising a transparent non-porous or translucent non-porous system capable of retaining or containing a fluid or solution. The system comprises a double-stranded oligonucleotide or polynucleotide which is directly or indirectly fixed or immobilized to the system wherein one of the strands produces a soluble signal generated or generatable from a chemical label or labels which comprise a signalling moiety or moieties. As set forth in the next paragraph, this subject matter is supported variously in the specification.

Continuing in Subparagraph A, Dr. Engelhardt writes:

> In the specification, the second paragraph on page 14, there is disclosed:
>
> > A further aspect of the present invention provides products useful in the disclosed method for detection of a polynucleotide sequence. Among these products is a

> device containing a portion for retaining a fluid. Such portion contains an immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe. The probe, as described above, has covalently attached thereto a chemical label including a signalling moiety capable of generating a soluble signal. Also part of the device is a soluble signal, preferably a colored or fluorescent product, generatable by means of the signalling moiety. The portion of the device for containing the fluid is desirably a well, a tube, or a cuvette. A related product of the invention is an apparatus comprising a plurality of such devices for containing a fluid, in which at least one such device contains the above-described immobilized polynucleotide sequence, polynucleotide or oligonucleotide probe, signalling moiety, and soluble signal.

According to Dr. Engelhardt:

> That above-quoted disclosure clearly indicates that the double-stranded oligonucleotide or polynucleotide can be fixed or immobilized to the system, be it a product, device, apparatus, wells, tubes, cuvettes, and the like. As such, the specification would reasonably convey to one skilled in the relevant art to which the present invention pertains that the subject matter of claims 77-85 and 86-99 was in the inventors' possession when the application was filed.

In Subparagraph B of his Declaration, Dr. Engelhardt indicates:

> My opinion expressed in the preceding paragraph is also bolstered by the original claims that were filed. In both originally filed claims 20 and 23, a device and an apparatus are claimed, respectively, in which an immobilized polynucleotide sequence is hybridized to a polynucleotide or oligonucleotide probe, without *any* recitation or reference to a solid support. The text of original claims 20 and 23 follows below:
>
> 20. A device which comprises:
> means for containing a fluid comprising:
> (i) an immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe, said probe having covalently attached thereto a chemical label comprising a signalling moiety capable of generating soluble signal, and
> (ii) a soluble signal generated by means of said signalling moiety.
>
> 23. An apparatus comprising:
> a plurality of means for containing a fluid, wherein at least one of said means comprises:
> (i) an immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe, said probe having covalently attached thereto a chemical label comprising a signalling moiety capable of forming a soluble signal, and
> (ii) a soluble signal generated by means of said signalling moiety.

In Dr. Engelhardt's opinion, "the originally filed claims, taken alone or with other

portions in the specification, for example, page 14, second paragraph, conveys to one skilled in the relevant art that the inventors possessed the subject matter of claims 77-85 and 86-99, wherein an oligonucleotide or polynucleotide is fixed or immobilized to the system as set forth in the claims at hand.

Finally, in Paragraph 9, Dr. Engelhardt concludes that "on the basis of the foregoing remarks and above-quoted portions from the specification that the original disclosure reasonably conveys to one skilled in the relevant art that at the time their application was filed, the inventors were in possession of the subject matter of claims 60 and 114, and 77-85 and 86-99.

[6] With the cancellation of claim 101 above, the ground of rejection for instructions being included with the kit has been rendered moot.

In view of the foregoing remarks, claim amendments and cancellation of claim 101, Applicants respectfully request reconsideration and withdrawal of the new matter rejection.

The First Anticipation Under 35 U.S.C. §102(b)

Claims 48-50, 53-56, 59, 61, 63-81, 84, 86-100, 102-104, 107-109, 113, and 115-132 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kourilsky et al. (UK 2,019,408). In the Office Action (pages 4-5), the Examiner stated:

> Kourilsky et al. disclose the preparation of various probes which hybridize to target nucleic acid on page 3. In particular cytochrome C is utilized to attach biotin to a probe. Beta-galactosidase is linked to the hybridized probe via avidin which is then centrifuged as given on said page 3, lines 42-49. Centrifuge tubes are inherently either glass or plastic. The pellet from this centrifugation is the practice of at least temporarily fixing the probe with enzymatic label onto a solid support device or system. The pellet is resuspended and optically assayed in solution for the enzymatic activity of the beta-galactosidase. This reads on the instant claims.
>
> Applicants argue the below art rejections in that the practice of in-situ hybridization is a very specialized type of methodology and different from the soluble signal generation practice as instantly claimed. In response applicants are reminded that compositions, apparati, and systems are claimed and not methods. Therefore, if a

> reference meets the composition, apparatus, or system limitations, it anticipates the instant invention even if a number of uses can be practiced for the claimed invention. In other words patentable weight is not given to use limitations if they do not limit the actual composition etc. limitations.

The rejection for anticipation by Kourilsky et al. is respectfully traversed.

It is respectfully submitted that Kourilsky's disclosure cannot properly sustain the anticipation rejection. In this regard, Applicants direct attention to the latter half of Dr. Engelhardt's Declaration (Exhibit 4) that addresses this anticipation rejection and the Kourilsky patent.

As indicated in his Declaration (Paragraph 11), it is Dr. Engelhardt's opinion and conclusion that Kourilsky's disclosure does not teach or suggest the present invention at hand because it fails to generate *any* soluble signal where the biotin labeled RNA is hybridized to the mouse DNA and when fixed or immobilized to a solid support. Dr. Engelhardt quotes from the Examiner in the January 21, 1998 Office Action:

> ". . . The pellet from this centrifugation [Kourilsky et al.] is the practice of at least temporarily fixing the probe with enzymatic label onto a solid support device or system. The pellet is resuspended and optically assayed in solution for the enzymatic activity of the beta-galactosidase. . ."

But Dr. Engelhardt points out that Kourilsky's disclosure is fatally flawed by its clear lack of any solid support so much so that they have to subject their sample to drastic ultracentrifugation in order to separate hybridized RNA-DNA from unhybridized nucleic acids. He also points out that it is only due to centrifugal force that any pellet is formed within the centrifugation tube, and the formation of that pellet does not constitute fixation or immobilization as it is understood in the field of nucleic acid technology or the present invention. According to Dr. Engelhardt, Kourilsky's use of ultracentrifugation prevents altogether *any* generation of a soluble signal from the pellet (Kourilsky et al. term it a "culot") which is not fixed or immobilized to any solid support, including the walls of the centrifugation tube. In fact, Kourilsky's disclosure specifically calls for resuspension in order to dislodge the pellet from the centrifugation tube wall. According to Dr. Engelhardt, in no sense does pelleting as it occurs during centrifugation constitute fixation or immobilization. In contrast to Kourilsky's

disclosure, the present invention provides for a soluble signal that is generate or generatable from a fixed or immobilized chemically labeled oligonucleotide or polynucleotide. Thus, and this is stated in the Engelhardt, Kourilsky et al. in no way generates or can generate a soluble signal from their biotin-labeled RNA-mouse DNA hybrid that is pelleted by means of ultracentrifugation and resuspended (detached) before assaying for beta-galactosidase activity. According to Dr. Engelhardt, it is impraticable if not impossible to generate a soluble signal from Kourilsky's pelleted product. Dr. Engelhardt notes that he is not aware of any instance or report where a soluble signal was generated from a pelleted product such as disclosed in Kourilsky's patent.

Continuing in Paragraph 12 of his Declaration, Dr. Engelhardt writes that in addition to the lack of a solid support or system for fixing or immobilizing the labeled RNA-DNA hybrid, there are other deficiencies in Kourilsky's disclosure that prevent if not severely limit the generation of a soluble signal. For one, Kourilsky et al. terminally label their RNA with pancreatic ribonuclease. This is disclosed on page 3 of Kourilsky's disclosure:

> Experiments were carried out on the model consisting of detecting the presence of a mouse DNA by hybridization of this DNA with a mouse ribosomic RNA used as a probe.
>
> Mouse DNA (100 µg per 100 µl of aqueous solution) is denatured by addition of soda (10 µl of 1 M NaOH). 10 minutes later, the solution was brought back to pH neutral by the addition of 10 µl of 1.5 M acid sodium phosphate NaH_2PO_4.
>
> 1 µg of ribosomic RNA labelled with biotin by means of cytochrome C, prepared by the technique of Manning & Coll., is added to the denatured DNA solution. This volume was adjusted to 160 µl with water. 40 µl of a solution having a concentration of mineral salts equal to twenty times that of the solution called SSC (abbreviation of the English expression "standard saline citrate") and 200 µl of redistilled or deionized formamide was then added to the medium. It is recalled that the SSC solution is an aqueous solution of 0.15 M sodium chloride, 0.015 M sodium citrate, at pH 7.0.
>
> The mixture was incubated until the next day at ordinary temperature, then dialyzed at 4° against a solution having a double concentration of the SSC solution, then for 8 hours against 500 ml of a phosphate buffer at pH 7.0 containing phosphate at a concentration of 0.1 M, sodium chloride at a concentration of 1 M and ethylene-diamine-tetrasodium acetate (EDTA) at a concentration of 0.01 M. The latter dialysis is then repeated twice, each time for 8 hours.
>
> The solution thus-obtained **was treated with *pancreatic ribonuclease*** for 1 hour at ordinary temperature, to obtain a final concentration of 10 µg per ml of ***ribonuclease***, this treatment permitting the degradation of the non-hybridized RNA.

> To the medium obtained was then added a solution of cytochrome C (1 mg per ml) and I microliter of a solution containing 1 mg per ml of avidin and 2 mg per ml of β-galactosidase, of which 1 molecule of β-galactosidase in seven is coupled with avidin. It is mixed and the solution is then left to stand at 4°C for 4 hours. The medium was then diluted to 10 ml with the phosphate dialysis buffer and the solution obtained is subjected to ultracentrifugation for 1 hour at 35,000 rpm (in a BECKMAN ROTOR SW 4.1 centrifuge) "BECKMAN" is a registered Trade Mark. The DNA and the hybridized RNA are to be found in the centrifugation culot, as well as the avidin-β-galactosidase bound to the RNA. The supernatant liquor contains the non-hybridized RNA degraded by the ribonuclease and the unbound avidin β-galactosidase. [emphasis added]

Dr. Engelhardt believes that there is sufficient breathing at the ends of any hybridized RNA-DNA that the ribonuclease can cut off the biotin label, thereby preventing detection of the hybrid.

In view of the deficiencies and lack of the instantly claimed material elements as described in the Engelhardt Declaration (Exhibit 4), Applicants respectfully request that the anticipation rejection by Kourilsky et al. be reconsidered and withdrawn.

The Second Anticipation Under 35 U.S.C. §102(b)

Claims 48-54, 56, 59, 61-79, 84-100, 102-108, 113, and 115-132 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Stuart et al. In the Office Action (page 5), the Examiner stated:

> Applicants argue that Stuart et al. is concerned with in situ hybridization and not applicable. This is non-persuasive as already discussed above. Applicants then argue that the instant invention requires chemically labeled nucleic acid for one of the strands. This is also non-persuasive because there is therein no limitation regarding whether a label may or may not also interact with the second strand in a hybrid formed during a hybridization assay. This rejection is reiterated and necessitated by amendment due to the newly added claims.

The second anticipation rejection is respectfully traversed and will be addressed below in conjunction with the other remaining anticipation rejections.

The Third Anticipation Under 35 U.S.C. §102(b)

Claims 48-54, 56, 59, 61-79, 84-100, 102-108, 113, and 115-132 stand rejected under 35 U.S.C. §102(a) as being allegedly anticipated either by Langer-Safer et al. or Manuelidis et al. In the Office Action (page 6), the Examiner stated:

> The listed claims are anticipated either by Langer-Safer et al. or Manuelidis et al. in the same manner as the above rejection based on Stuart et al. because both references also discussed the performance of in situ hybridization of chromosome spreads on microscope slides etc. as summarized above. This rejection is reiterated and necessitated by amendment due to the newly added claims.

The third anticipation rejection is respectfully traversed and will also be addressed below.

The Fourth Anticipation Under 35 U.S.C. §102(b)

Claims 48-132 stand rejected under 35 U.S.C. §102(e) as being anticipated by Ward et al. In the Office Action (page 6), the Examiner stated:

> Ward et al. disclose via the "GENERAL PROTOCOL" and with connected discussion elsewhere at the bottom of columns 19 and 20 in situ hybridization where immobilized double-stranded nucleic acid is shown visualized with a biotinylated probe bound to avidin-peroxidase. This reads on the listed claims as the peroxidase is capable of generating a soluble signal as discussed above and therefore still reads on the instant invention even though Ward et al. discloses insoluble signal generation. This rejection is reiterated and necessitated by amendment due to the newly added claims.

The fourth anticipation rejection is respectfully traversed and is addressed below.

With respect to the *in situ* references exemplified by Stuart et al., Langer-Safer et al., Manuelidis et al. and Ward et al., Applicants respectfully maintain that none of these documents disclose or otherwise suggest the instantly claimed elements of a system for containing a fluid or solution, and the positively recited element of a soluble signal generated or generatable from a chemical label or labels comprising a signaling moiety or moieties. It is respectfully requested, therefore,

that the second, third and fourth anticipation rejections be reconsidered and withdrawn on the basis of a lack of identity of material elements with the instant invention.

The Rejection for Obviousness-Type Double Patenting

Claims 48-132 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-19 of U.S. Patent No. 4,994,373. In the Office Action (page 7), the Examiner stated:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain common embodiments regarding devices, compositions, apparati, and kits. It is noted that a terminal disclaimer was filed in the immediate parent to the instant application, however, when a new application serial number is utilized due to the instant application being a continuation of saod parent a new terminal disclaimer must be filed.

The double patenting rejection is respectfully traversed.

Applicants' attorneys and the instant Assignee have carefully considered the obviousness-type double-patenting rejection in light of the statutory provisions of 35 U.S.C. §121, applicable caselaw and a thorough review of the prosecution history of this application. Based upon this analysis, it is believed that the double-patenting rejection is improper. The reasons why the rejection is improper is as follows.

The ability of the PTO to issue a double patenting rejection is limited by the provisions of 35 U.S.C. §121. This statute has two components. The first provides the Commissioner of Patents & Trademarks with the power to order "restriction" of an application that is directed to two or more "independent and distinct" inventions so that its claims are directed to only one of the inventions. This provision serves the purpose of ensuring that each patent is directed to only one invention, and thus facilitates proper examination of patent applications. It should be pointed out that the decision *not* to restrict the claims of a patent application is committed to the discretion of the Commissioner, and a patent cannot be invalidated due to the Commissioner's failure to issue a restriction requirement. 35 U.S.C. §121. The PTO interprets the term "independent" to mean

that the inventions are unconnected in design, operation or effect. It interprets the term "distinct" to mean that the inventions are capable of separate manufacture, use or sale. Following these definitions, a method would be independent and distinct from a reagent if the reagent may be used in other methods, and if the method may be practiced with other reagents. A claim to a modified nucleotide *per se* would be independent and distinct from a method that uses the modified nucleotide if the method can be practiced with other nucleotides, or if the modified nucleotides could be used in a different method.

The second component of 35 U.S.C. §121 mandates that, if the Commissioner has restricted an application, neither he, nor the Federal Judiciary, can cite one "divisional" application as a reference against the other. This second component is embodied in the statute and deserves quoting therefrom:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.
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> [35 U.S.C. §121]

Thus, by the clear express language of the statute, one cannot issue a double patenting rejection on an application in view of the issuance of any of its divisionals.

To establish the impropriety of the double-patenting rejection at hand, one must perform a two-prong test. First, one must determine that a restriction requirement was previously made by the PTO, and second, one must shown that the present application is a *bona fide* divisional of the application ultimately issuing as the '373 Patent. The second prong can be established by demonstrating that the pending claims conform to a group or groups in the restriction requirement that were not present in the issued '373 Patent claims.

File Histories Relating to U.S. Patent No. 4,994,373 and Serial No. 08/486,070

Both the '373 Patent and Serial No. 08/486,070 trace their origins to U.S. Patent Application Serial No. 06/461,469, filed on January 27, 1983. On June 13,

1984, the PTO issued an office action to require restriction of the then-pending claims, indicating that the following five groups are different and distinct inventions:

> I. Claims 1-11, 19-51, 69-71, 81-82, 85-86, 96-98, 100, 104-105, and 107-109, drawn to a substrate to which a polynucleotide is fixed, classified in Class 435, subclass 188.
>
> II. Claims 12-18, 52-62, 72, 74-80, 83-84, 87-95 and 99, drawn to an assay for detecting pathogens which utilizes nuclear hydrization(sic), classified in Class 435, subclass 6.
>
> III. Claims 64, 65, 68 and 73, drawn to laboratory apparatus, classified in Class 422, subclass 99.
>
> IV. Claims 63, 66-67, drawn to a coating process, classified in Class 427, subclass 299+.
>
> V. Claims 101-103 and 106, drawn to a device for measuring a chemical reaction, classified in Class 435, subclass 287.

In that June 13, 1984 Office Action, the examiner supported the restriction requirement with the following remarks:

> The inventions are separate and distinct, each from the other because of the following reasons:
>
> Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as measuring gene expression in cells, detecting messenger RNA, etc.
>
> Inventions II and V are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP 806.05(e)). In this case the apparatus as claimed can be used to practice another materially different process such as an immunoassay utilizing an enzyme label.
>
> Inventions I and III are related as a product and apparatus used to make the product. The product of Group I can be attached to other surfaces such as plastic, nitrocellulose, etc.
>
> Inventions III and IV are related as an apparatus and process of preparing the apparatus. The process of Group IV can be utilized to prepare surfaces for attachment of other substances such as proteins, etc.
>
> Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

In the subsequent office action issued on November 9, 1984, the same examiner made the restriction requirement final, stating:

> Claims 12-18, 52-68, 72-80, 83-84, 87-95, 99, 101-103 and 106 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10.
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> Applicant's election with traverse of Invention I in Paper No. 10 is acknowledged. Applicant's argument is not deemed persuasive because applicants' reason given to urge that the application not be restricted do not appear to address the issues of separateness and distinctness (See paragraph bridging page 2 and 3 of the restriction requirement Paper No. 9). Additionally, contrary to applicants' statements, the examination of the claims drawn to Inventions II-V would place an undue burden upon the Examiner since these inventions have acquired a separate status in the art due to their divergent subject matter.
>
> The requirement is still deemed to be proper and is therefore made FINAL

Serial No. 06/461,469 was refiled as a continuation-in-part application on May 9, 1985, being accorded Serial No. 06/732,374. The latter was refiled on July 20, 1989 as a continuation application and accorded Serial No. 07/385,986, which issued as the '373 Patent on February 19, 1991. The '373 Patent issued with claims directed to a method for detecting a polynucleotide sequence (claims 1-16 and 20-27), a device for detecting a polynucleotide sequence according to the method of claim 1 (claim 17), and a kit for detecting a polynucleotide sequence (claims 18-19). The issued claims of the '373 Patent conform to the June 13, 1984 restriction requirement insofar as the method claims (1-16 and 20-27) represent an assay for detecting pathogens or Group II as delineated by the examiner at that time. The kit claims (18-19) are also believed to be properly part of Group II, although kit claims were not pending at that time, nor were they discussed in conjunction with the restriction requirement. The device of claim 17 would appear to be properly part of Group V, a device for measuring a chemical reaction.

On October 30, 1990, a continuation application of Serial No. 07/385,986 was filed, being accorded Serial No. 07/607,347. On

December 17, 1991, the present Examiner issued an office action in which a previously presented claim was withdrawn from consideration as being directed to a non-elected invention. In the December 17, 1991 Office Action, the Examiner supported his position on the restriction issue indicating:

> Newly submitted claim 35 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:
>
> Inventions of claims 27-30 with 32-34 and claim 35 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using the product (M.P.E.P. § 806.05(h)). In the instant case the claimed product can be used in a materially different process which is for the purification of nucleic acids by affinity chromatography.
>
> Inventions of claim 35 and claim 31 are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (M.P.E.P. § 806.05(e)). In this case the apparatus can be used to practice another and materially different process which is purification of nucleic acids by affinity chromatography.
>
> Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.
>
> Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 35 is withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

An Advisory Action was subsequently issued on April 6, 1992 in which it was indicated under box 4 that "[t]he restriction requirement is also maintained and discussed as attached." Under box 5 of the Advisory Action, it was indicated that "[n]ote that claim 35 remains withdrawn from consideration as being directed to a non-elected invention."

Because the June 13, 1983, November 9, 1984 and December 17, 1991 Office Actions and the April 6, 1992 Advisory Action are part of the file histories of related predecessor applications, Applicants have not included copies with this

Amendment. In the event, however, that the Examiner is unable to obtain these documents from the PTO files, Applicants' attorney would willingly furnish copies upon request.

With respect to the claims at hand, it is believed that pending claims 48-100 and 102-179 belong to groups set forth in the June 13, 1984 restriction requirement that were not covered by the issued claims of the '373 Patent. As indicated above, the issued claims of the '373 Patent conform to Group II and Group V set forth in the June 13, 1984 restriction requirement. That is to say, the issued method claims (1-16 and 20-27) and the kit claims (18-19) represent an assay for detecting pathogens (Group II). The device of issued claim 17 represent a device for measuring a chemical reaction (Group V). Among the pending claims, all of these belong to the other groups as listed in the June 13, 1984 restriction requirement:

Pending Claims	Subject Matter	June 13, 1984 Restriction Requirem't	
claims 48-99, 133-136, 138-139	composition	Group I	substrate to which polynucleotide is fixed
claims 102-131, 137 and 140	system	Group I	substrate to which polynucleotide is fixed
claims 141-179	array	Group I	substrate to which polynucleotide is fixed
claims 100 and 132	apparatus	Group III	laboratory apparatus

As can be seen in the chart above, the pending claims fall into either Group I or Group III of the June 13, 1984 restriction requirement, and they do not overlap with the issued claims of the '373 Patent, those latter claims falling into Group II or Group V of the restriction requirement. Thus, the instant application properly constitutes a divisional of the then-pending application for the '373 Patent. As such, an obviousness-type double-patenting rejection of the pending claims in view of the issued '373 Patent claims is improper. As set forth above, 35 U.S.C. §121 mandates that, if an application has been restricted, a divisional application

conforming to the restriction cannot be cited against the other. Accordingly, the issued claims of the '373 Patent cannot be cited against the pending claims.

In light of the prosecution history relating to the present application and U.S. Patent No. 4,994,373, the express language of the statute (35 U.S.C. §121), Applicants respectfully request reconsideration and withdrawal of the obviousness-type double-patenting rejection.

Correction of Informalities

On pages 7 and 8 in the Office Action, the Examiner objected to the disclosure because of informalities relating to the use of the trademark TRITON X-100. The Examiner pointed out that the trademark should be capitalized wherever it appears and be accompanied by the generic terminology, citing, for example, page 24, lines 9-10, 22, and 30.

As indicated in the opening remarks of this Amendment, the specification has been amended in several instances to correct the informalities relating to the TRITON® trademark.

* * * * * * *

SUMMARY AND CONCLUSIONS

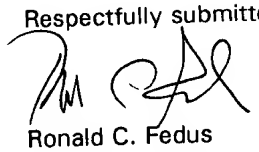
Claims 48-100 and 102-182 are presented for further examination. Claims 48, 55, 63, 77, 80, 86, 100, 102, 109, 118 and 132 have been amended. Claim 101 has been canceled. New claims 133-182 have been added.

This Amendment is being accompanied by Applicants' Request For An Extension Of Time (3 months) and authorization for the fee therefor. Furthermore, the accompanying Transmittal to this Amendment further authorizes the payment of $1,160 for the additional 49 new claims and 1 new independent claim taking into account one canceled claim. No other fee or fees are believed due. In the event, however, that any other fee or fees are due in connection with this Amendment, the extension request or the additional claims, the Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting the prosecution of this application, the undersigned may be contacted by telephone at 212-583-0100 during the daytime business hours.

Early and favorable action on this application is respectfully sought.

Respectfully submitted



Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO DIAGNOSTICS, INC.
c/o Enzo Biochem, Inc.
527 Madison Avenue (9th Floor)
New York, New York 10022
Telephone: (212) 583-0100
Facsimile: (212) 583-0150